REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on October 16, 2008.

Claims 8-9 and 24 had been pending and were examined. Claims 1-7 and 10-23 were previously cancelled without prejudice or disclaimer. Claim 9 has been cancelled in this paper without prejudice or disclaimer, and claims 8 and 24 have been amended.

Claim 8 has been amended to recite "a) bringing into contact the lysophosphatidic acid and the EDG-2 receptor and measuring the binding property of the lysophosphatidic acid and the EDG-2 receptor; b) bringing into contact the lysophosphatidic acid, the EDG-2 receptor, and the test compound and measuring the binding property of the lysophosphatidic acid and the EDG-2 receptor; c) measuring the effect of the test compound on the binding activity of the lysophosphatidic acid and the EDG-2 receptor by comparing a) and b)." Support for the amendment is found in the specification as filed, for example, at least at page 34, lines 2-9. Claim 24 has been amended to recite "administering the test compound that changes the binding property of the lysophosphatidic acid and the EDG2 receptor and that inhibits mesangial cell growth to an animal model for diabetic nephropathy, chronic renal failure, nephritis, glomerulonephritis, interstitial renal disease or renal edema." Support for that amendment is found in the specification, for example, at least at page 8, lines 1-15; page 26, lines 6-11; page 60, lines 6-11; and page 63, line 29-page 64, line 8. Accordingly, the amendments to claims 8 and 24 are fully supported by the specification as filed and no new matter has been added. Upon entry of the present amendments, claims 8 and 24 will be under consideration.

Applicants address below each issue raised in the Office Action of October 16, 2008.

Preliminary Matters

Applicants note with appreciation that the Office has withdrawn the finality of the previous Office Action and entered Applicant's submission filed on August 26, 2008.

Applicants also note with appreciation that the Office appears to have withdrawn the previous rejections under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 102(b), and 35 U.S.C. § 102(e).

Claim Rejections

I. Rejections of Claims 8, 9, and 24 under 35 U.S.C. § 112, Second Paragraph

Claims 8, 9, and 24 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "incomplete for omitting essential steps, such omission amounting to a gap between the steps." Action at page 2. The Office stated that the "method steps a-c in the independent claim 8 seem to lack an intermediary step because it is not possible to measure the initial binding of LPA to EDG-2 receptor once the test compound is brought in the measuring mix." *Id.*

Applicants respectfully traverse. Solely to facilitate prosecution, and not in acquiescence of the rejection, Applicants have amended claim 8 to recite:

> a) bringing into contact the lysophosphatidic acid and the EDG-2 receptor and measuring the binding property of the lysophosphatidic acid and the EDG-2 receptor;
>
> b) bringing into contact the lysophosphatidic acid, the EDG-2 receptor, and the test compound and measuring the binding property of the lysophosphatidic acid and the EDG-2 receptor;
>
> c) measuring the effect of the test compound on the binding activity of the lysophosphatidic acid and the EDG-2 receptor by comparing a) and b);
>
> d) determining whether the test compound changes the binding property of the lysophosphatidic acid and the EDG-2 receptor. . . .

Thus, claim 8 does not lack an intermediary step.

Claim 24 was also rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Action at page 3. The Office stated that "it is unclear if the animal in part (a) has to have a condition that needs improvement." *Id.*

Applicants respectfully traverse. Solely to facilitate prosecution, and not in acquiescence of the rejection, Applicants have amended claim 24 to recite " administering the test compound that changes the binding property of the lysophosphatidic acid and the EDG2 receptor and that inhibits mesangial cell growth to an animal model for diabetic nephropathy, chronic renal failure, nephritis, glomerulonephritis, interstitial renal disease or renal edema." Accordingly, claim 24 is not indefinite.

For at least those reasons, Applicants respectfully request withdrawal of the rejections.

II. Rejection of Claim 9 under 35 U.S.C. § 102(e)

Claim 9 was rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Goddard et al. (U.S. Patent 6,949,528). The Office stated that claim 9 "is interpreted as being drawn to a composition comprising lysophosphatidic acid and a buffer" and that the "intended use and the printed instructions are not given patentable weight for the claim." Action at page 3. The Office also stated that Goddard teaches "compositions comprising lysophosphatidic acids and buffers." *Id.*

Applicants respectfully traverse. Nonetheless, solely to facilitate prosecution and not in acquiescence to the rejection, claim 9 has been cancelled without prejudice or disclaimer, rendering the rejection moot. Applicants respectfully request withdrawal of the rejection.

III. Rejection of Claims 8, 9, and 24 under 35 U.S.C. § 103(a)

Erickson, Lynch, and Inoue

Claims 8 and 24 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Erickson et al. (U.S. Patent 6,485,922) in view of Lynch et al. (U.S. Patent No. 7,169,818) and Inoue, "LPA as a Determinant of Mesangial Growth and Apoptosis" *Semin Nephrol.* 22(5):415-422 (2002).

According to the Office, Erickson teaches "a method for identifying compounds which modulate the activity of the EDG receptors, comprising the steps of exposing a compound and LPA to the EDG-2 receptor coupled to a response pathway, under conditions and for a time sufficient to allow interaction of LPA with the EDG-2 receptor and an associated response through the pathway and b) detecting an increase or a decrease in the stimulation of the response pathway, relative to the absence of the tested compound." Action at pages 5-6. The Office stated that "[s]ince the detection of any activation of the EDG-2 receptor is necessarily linked to the binding of the LPA to the EDG-2 receptor, the limitations of claim 8 [are] present in Erickson." *Id.* at page 6. The Office indicated that "Erickson is silent about the use of the method applied to mesangial cells as a two step process and further improvement of renal conditions upon the use of the antagonist." *Id.*

The Office contended that Lynch "teach[es] a method of assaying the binding of agonist[s] or antagonists of LPA for the activation of LPA receptors and thus allow[s] the identification of LPA receptor agonists and antagonists as well as determination of the relative efficacies and potencies at each receptor in a common system." Action at page 6. The Office stated that Lynch obtained the same results "regardless of whether the recombinant receptor used exogenous G proteins (HEK293T cells) or endogenous G proteins (RH7777 cells)" and that "the

activities measured in the broken cell assay predicted the responses seen in whole cell assays." *Id.* The Office concluded that Lynch "teaches the confirmation of the results obtained in the absence of living cells in the context of a living cell." *Id.* Furthermore, the Office urged that the "findings from the in vitro (broken cells assays) were predictive for the success of the method in the cell culture assays and thus the method could be reasonabl[y] expected to work in animal test[s] also." *Id.* at pages 6-7.

The Office stated that Inoue teaches that LPA plays a role "in regulating renal mesangial cells[']' growth and apoptosis by stimulating the EDG-2 receptor (p. 415, right col. and Fig. 3)" and that "the inappropriate equilibrium of mesangial cell growth and death resulting from improper blockage of apoptosis induced by LPA is involved in the etiology of glomerulonephritis." Action at page 7.

Thus, the Office concluded that a "person of ordinary skill in the art would realize, based upon Inoue et al., that blocking the effects of LPA on mesangial cells would have had beneficial effects for the renal diseases in which overgrowth of mesangial cells have been involved." Action at page 7. Furthermore, the Office contended that "a person of ordinary skill in the art would have been motivated to use the methods of Erickson et al. and Lynch et al. to look for antagonists of LPA with a reasonable expectation of success, given also the teachings of Inoue . . . because the method was successfully used to find compounds that inhibited LPA binding to its receptor and the use of mesangial cells would have represented one of the possibilities of testing in conditions with the receptor would have been part of the cell membrane." *Id.*

Applicants respectfully traverse. The Supreme Court recently reaffirmed the framework set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) for applying the statutory language of 35 U.S.C. § 103:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. *Id., at 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545.*

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1 727, 1734 (2007), quoting *Graham*, 383 U.S. at 17-18. The Supreme Court further explained that "the factors continue to define the inquiry that controls." *Id.*

The *Graham* test reinforces Applicants' assertion that the claims are not obvious. Contrary to the Office's position, the cited documents do not teach or suggest:

> f) bringing into contact a mesangial cell expressing the EDG-2 receptor, lysophosphatidic acid, and the test compound of step d) determined to change the binding property of the lysophosphatidic acid and the EDG-2 receptor and measuring mesangial cell growth;
>
> g) measuring the effect of the test compound on mesangial cell growth by comparing e) and f); and
>
> h) determining whether the test compound inhibits mesangial cell growth.

As the Office stated, "Erickson is silent about the use of the method applied to mesangial cells as a two step process and further improvement of renal conditions upon the use of the antagonist." This deficiency is not remedied by Lynch or Inoue, either alone or in combination. Nothing in Lynch and Inoue teaches or suggests a connection between Edg-2 and mesangial cell growth. Moreover, they suggest that either Edg-7 or Edg-4 may be involved in kidney cell

growth. Thus, one skilled in the art would not be motivated to screen for a test compound that changes a binding property of LPA to an Edg-2 receptor and that inhibits mesangial cell growth, as claimed. Instead, based on the teachings of these cited references, one skilled in the art would be more likely to be motivated to screen for a test compound that affects binding to the Edg-4 or Edg-7 receptor.

For example, Lynch does describe assays testing "efficacies and potencies" of LPA analogs on Edg receptor-transfected human embryonic kidney (HEK293T) cells and rat hepatoma (RH7777) cells. However, Lynch recognizes that LPA uses multiple receptors and suggests that it is largely unknown which individual receptors are responsible for a given physiological effect. For example, Lynch states that "LPA signals cells in part via a set of G protein-coupled receptors named LAP1, LPA2, and LPA3 (formerly Edg-2, Edg-4, and Edg-7)." Lynch at col. 1, lines 53-55. Lynch also states that the "physiologic implications of individual LPA receptors are largely unknown due in part to a lack of receptor type selective ligands." *Id.* at col. 1, line 66 to col. 2, line 1. Indeed, Lynch further states that LPA "elicits a wide variety of responses from cells and tissues including calcium mobilization, changes in cell shape and motility, mitogenesis and anti-apoptosis. These effects are mediated by at least three LPA receptors." *Id.* at col. 4, lines 48-52. In addition, Lynch does not teach or suggest a connection between Edg-2 and mesangial cells. According to Lynch, "LPA1[, i.e., Edg-2] is most associated with activation of Giα pathways and is expressed in oligodendrocytes and peripheral tissues while . . . **LPA3[, i.e., Edg-7]** mRNA has been localized to prostate, testes, pancreas, **kidney**, and heart." *Id.* at lines 59-65 (emphasis added).

The Office points to the right column of page 415 and Figure 3 of Inoue to support the contention that LPA plays a role "in regulating renal mesangial cells[*] growth and apoptosis by

stimulating the EDG-2 receptor (p. 415, right col. and Fig. 3)." However, neither the right column of page 415 nor Figure 3 support that conclusion. Inoue does state that "Edg-2, -4, and -7 predominantly use LPA as their endogenous ligands." Inoue at page 415, right column. However, nothing in Inoue teaches or suggests that LPA binding to Edg-2 regulates mesangial cell growth or apoptosis. Figure 3 shows that "LPA suppresses both mesangial cell death evoked by PDGF or by serum withdrawal." Inoue at page 418, legend for Figure 3. However, Inoue does not discuss whether that suppression of cell death is attributable to Edg-2 or another LPA receptor. While Inoue notes that "both Edg-2 and Edg-4 mRNAs are abundantly expressed in primary cultured human mesangial cells," Inoue asserts that his group has found **Edg-4 mRNA**, but not Edg-2 mRNA, "to be highly expressed in renal glomeruli isolated from biopsy samples of patients with advanced mesangial proliferative glomerulonephritis of immunoglobulin A nephropathy." Inoue at page 421, left column. Furthermore, Inoue discusses that a "recent report further shows that LPA exerts Rho-mediated morphological changes in mesangial cells" and that "details of the classes of G proteins or signaling pathways that lead to these various LPA-induced mesangial responses remained to be fully understood." Inoue at page 420, left column. Thus, Inoue does not specifically attribute the physiological effects of LPA on mesangial cells to Edg-2. In fact, Inoue even teaches away from Edg-2 and suggests to one skilled in the art that Edg-4 may be the more likely candidate involved in kidney cell growth.

The Office also contends that "findings from the in vitro (broken cells assays) [of Lynch] were predictive for the success of the method in the cell culture assays and thus the method could be reasonabl[y] expected to work in animal test[s] also." Action at pages 6-7. However, the cited references do not provide any support for this conclusion. In fact, as discussed above, the combination of Erickson, Lynch, and Inoue do not tie together the physiological effects of LPA

on mesangial cells to Edg-2. Thus, there is no reasonable expectation that Lynch's methods could be extrapolated to "work in animal test[s]."

For the reasons discussed above, Erickson, Lynch, and Inoue, either alone or in combination, do not render the pending claims obvious. Applicants respectfully request withdrawal of the rejection.

Miller, Lynch, and Inoue

Claims 8 and 24 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Miller et al. (U.S. Patent 6,875,757) in view of Lynch et al. (U.S. Patent No. 7,169,818) and in further view of Inoue, "LPA as a Determinant of Mesangial Growth and Apoptosis" *Semin Nephrol.* 22(5):415-422 (2002).

The Office contended that Miller teaches a "method of modulating LPA activity on an LPA receptor which includes providing a compound which has activity as an LPA receptor antagonist and contacting an LPA receptor with the compound under conditions effective to inhibit LPA-induced activity of the LPA receptor." Action at page 8. The Office recognized that Miller "does not explicitly teach about the use of the method applied to mesangial cells, and for further determination of improvement of renal conditions upon the use of the antagonist." *Id.* The Office urges that "any activity through EDG-2 is in the wake of LPA binding to the EDG-2 receptor and thus the effects on any cells are expected to still be able to be blocked, irrespective of the cells that harbor the EDG-2 receptor." *Id.* at pages 8-9.

Regarding Lynch and Inoue, the Office pointed to its statements in the rejection over Erickson, Lynch and Inoue. *See* Action at page 9.

The Office concluded that "it would have been obvious for a person of ordinary skill in the art to block the effects of LPA on mesangial cells with beneficial effects for the renal

diseases in which overgrowth of mesangial cells have been involved . . . with reasonable expectation of success." Action at page 9. As support, the Office states that "the methods of Miller et al. and Lynch et al. were intended to uncover LPA binding blockers in general and it would have the antagonistic effect everywhere the signal transduction pathways through EDG-2 receptors would have occurred in response to LPA binding." *Id.* The Office also states that "the teachings of Inoue et al. would have motivated a person of ordinary skill in the art to use mesangial cells for testing modulators of LPA/EDG-2 interaction." *Id.*

Applicants respectfully traverse. As recognized by the Office, Miller "does not explicitly teach about the use of the method applied to mesangial cells, and for further determination of improvement of renal conditions upon the use of the antagonist." As discussed above, Lynch and Inoue do not tie together the physiological effects of LPA on mesangial cells to Edg2. Moreover, Lynch and Inoue suggest that Edg-7 or Edg-4, respectively, may be the more likely candidates that mediate kidney cell growth. Thus, one skilled in the art would not have been motivated to screen for a test compound that changes a binding property of LPA to an Edg-2 receptor and inhibits mesangial cell growth, as claimed. Rather, one skilled in the art may have been more likely to screen for a test compound that affects other Edg receptors, not the Edg-2 receptor, based on the teachings of Lynch and Inoue. Accordingly, Miller, Lynch, and Inoue, either alone or in combination, do not render the pending claims obvious. Applicants respectfully request withdrawal of the rejection.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any further extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 31, 2009

By: _____
Yuko Soneoka
Reg. No. 60,018
Customer No. 22,852